REMARKS

I. Status of the Claims

Claims 1-8, 32, 41, 50, 60-62, 64, 73-81, 90 and 91 are pending. Claims 1-8 and 32 stand rejected. Claims 9-31, 33-40, 42-49, 52-59, 65-72 and 82-89 have previously been cancelled. No claims are amended.

II. Remarks

A. Rejections under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claims 1-8 and 32 as being allegedly unpatentable under 35 U.S.C. 103(a) over Richon et al. Proc. Natl. Acad. Sci. Vol. 95, pp. 3003-7 (1998) ("Richon") and WO0226696 to Watkins et al. ("Watkins"). Watkins describes carbamic acid compounds comprising an amide linkage that inhibit HDAC activity. *Watkins* at abstract. Richon describes hybrid polar compounds which inhibit HDAC. *Richon* at abstract.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.,* 383 U.S. 1 (1966); *see also* Fed. Reg. Vol. 72, No. 195, p. 57529. Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. The Examiner must also show that one of ordinary skill in the art would have a reasonable expectation of success in making the claimed modification. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. Applicants respectfully submit that the Examiner has not met this burden.

The Examiner alleges that Richon discloses a compound that is a homolog of the presently claimed compounds, with a difference of only one -CH_2- group. *Final Office Action* at p. 3. The Examiner contends that compound 7 of Richon reads on the claimed compound when R1 is phenyl, m is 0, and n is 5. Applicants note that m cannot be equal to 0 in the instant claims. Rather, m is equal to 1-10. Furthermore, the Board has held that a -CH_2- homolog does not necessarily render a claim obvious, without more. *Ex parte Goonewardene*, 160 U.S.P.Q. 287 (Bd. Pat. App. 1968).

Regarding Watkins, the Examiner points to allegedly "similar" compounds, and states "[c]learly the equivalency of the linkage to N or the Ch2 for the R1 is equivalent." *Final Office Action* at p. 4. Applicants disagree. Watkins merely describes regioisomers of an amide linkage. Nothing in Watkins, nor in the knowledge of the art, teaches or suggests such "equivalency" of -CH2- and N linkages. The Examiner provides no articulated reason or rational underpinning for this assertion, as required by *KSR*. Indeed, this merely a conclusory statement explicitly prohibited by the Supreme Court's *KSR* decision.

The Examiner then contends that based on the allegedly similar compounds of Richon and Watkins, "with the teaching of equivalence of the linkages, there is a motivation to modify them to obtain the compounds of the invention. *Final Office Action* at p. 5. Applicants submit that the Examiner has failed to provide any rational underpinning for this assertion motivation to modify these compounds, without the benefit of Applicant's present disclosure.

Additionally, Applicants direct the Examiner's attention to *Takeda v. Ranbaxy*, 492 F.3d 1350 (2007). In *Takeda,* applying *KSR*, the Federal Circuit stated " in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Id.* at 1361. Like Takeda, one of skill in the art would have had to select a lead compound out of Richon or Watkins as a starting point for modification. Nothing in Richon directs the skilled artisan to chose as a lead compound 7, which is relied on t by the Examiner. Likewise, nothing in Watkins directs the skilled artisan to any compounds 35, 41, 6, 36, or 37 as possible leads, out of the many disclosed compounds. The skilled artisan, after selecting a one of these compounds, would then, have to take the additional step of either homologation, in the case of the

Richon compound, or conversion of an amide to a urea linkage in the case of the Watkins compounds. Applicants submit that the Examiner has provided no rational for such selection and modification of Richon and Watkins, either alone or in combination.

For at least these reasons, Applicants submit that the present claims are not obvious over either Watkins or Richon, or the combination of these references.

B. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintains the rejection of claims 1-8 and 32 as being allegedly unpatentable under 35 U.S.C. § 112, first paragraph, for a lack of an enabling disclosure. *Advisory Action* at p. 2; *see also Final Office Action mailed on November 24, 2006*, p. 2. In the Final Office Action, the Examiner contends that the present rejection under § 112, first paragraph, is based on "make and use," and that Applicants have not enabled the use of these compounds because pharmaceutically uses are allegedly "unpredictable." *Final Office Action* at p. 3. Specifically, the Examiner contends that the specification "while being enabling for R1 to be a phenyl , does not reasonably provide enablement for any other cycloalkyl or any 3-10 membered heterocyclic group." *Office Action mailed May 8, 2006*. In the Advisory Action, the Examiner alleges, without any support, that "[a] heterocylic group or a cycloalkyl group would definitely be different than an phenyl or adamantyl and as such should have more showing that it is a 'pharmaceutical'" *Advisory Action* at p. 2. Applicants respectfully traverse this rejection.

35 U.S.C. §112, first paragraph, requires that a patent must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Nevertheless, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. § 2164.01. In order to make a rejection for lack of enablement, the Examiner bears the burden of establishing "a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04 (citing *In re* Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Furthermore, a specification "which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought must be taken as being in compliance with the enablement

requirement . . . , unless there is a reason to doubt the objective truth of the statements contained therein . . . ." M.P.E.P. § 2164.04. It is also well-established that Applicants need not "necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill in gaps." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

Applicants traverse this rejection. Applicants submit that the Examiner has failed to meet the above legal standard for finding a lack of enablement. Instead, the Examiner has applied an erroneous legal standard in rejection the present claims for lack of enablement, and has furthermore ignored Applicant's factual-based evidence of enablement. Under the Wands analysis, the present claims are more than sufficiently enabled, as explained below.

As the Examiner noted in the previous Office Action, several factors are considered in determining whether any experimentation is undue, including: 1) the breadth of the claims; 2) the nature of the invention; 3) the state of the prior art; 4) the level of one of ordinary skill; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor; 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737; M.P.E.P. 2164.01(a). Applicants further point out that 35 U.S.C. §112, first paragraph, requires that a patent must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Nevertheless, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. § 2164.01.

Regarding the first Wands factor, the Examiner contends that the claims encompass "very wide range of compounds." Applicants respectfully disagree that the present claims are unduly broad. Furthermore, as explained in more detail below, the breadth of the instant claims are fully enabled by the specification.

Regarding the second *Wands* factor, the nature of the invention, the Examiner merely states "the invention is a substituted compound that is useful to treat cancer." *Office Action mailed May 8, 2006*, at p. 3. The Examiner does not explain how this factor supports an enablement rejection.

Regarding the third *Wands* factor, the Examiner contends that the state of the prior art involves screening *in vitro* and *in vivo*, and that there is "no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way." *Action mailed May 8, 2006*, at p. 3 (emphasis added). Regarding the fifth *Wands* factor, the Examiner alleges that the pharmaceutical art is unpredictable, "requiring each embodiment to be individually assessed for physiological activity." *Office Action May 8,* 2006, at p. 3; *see also Final Office Action* at p. 3 (citing *In re Fisher*) (emphasis added). The Examiner further alleges that "there is no absolute predictability and no established correlation between in vitro activity and the treatment of any and all cancers." *Id.*

The Examiner's analysis of the third and fifth wands factors contains several erroneous legal standards. First, the Examiner's apparent requirement that Applicants individually assess each embodiment of the present claims has no basis in the law. Neither the M.P.E.P. nor the case law requires such a standard. The C.C.P.A. has explicitly stated that patent applicants are "**not required to disclose every species encompassed by their claims even in an unpredictable art**." *In re Angstadt*, 537 F.2d 489, 502 (C.C.P.A. 1976) (emphasis added). Working examples are not even necessarily required to enable an invention. *In re Long*, 368 F.2d 892, 895 (C.C.P.A. 1966)(holding that the absence of a working example does not in and of itself compel a finding of non-enablement). The Examiner misinterprets *In re Fisher*, 427 F.2d 833 (CCPA 1970). *Fisher* merely found that an applicant had not enabled the full claimed potency range of a particular compound. In particular, the applicant had disclosed a potency range of 1.11 to 2.30 international units, but tried to claim a range of greater than 1. The court found that the applicant in that case was not entitled to the open-ended range of greater than 1. Thus, the Examiner's reliance on *Fisher* for the proposition that each compound must be assessed for activity is in error. Applicants further submit that *Fisher* is not at all relevant to the present claims.

Additionally, "absolute predictability" is not required, nor must Applicants demonstrate that each compound "behave[s] in the exact same way." Applicants respectfully request that the Examiner apply the correct legal standard in assessing enablement.

Indeed, Applicants direct he Examiner's attention to the case law which has recognized the advances in the art with respect to cancer treatment. The C.C.P.A. noted in its decision in *In re Jolles* that "medical treatment of a specific cancer is not such an inherently unbelievable undertaking or involves such implausible scientific principles as to be incredible." *In re Jolles*, 628 F.2d 1322, 1327 (C.C.P.A.). The Board also has recognized that "[t]he state of the art of cancer treatment has advanced markedly since the time of the decision in *In re Citron* . . . as reflected in the decision *In re Jolles.*" *Ex parte Krepelka* U.S.P.Q. 746, 747 (Bd. Pat. App. & Int. 1986). Finally, the Federal Circuit in *In re Brana* noted that "[m]odern science has previously identified numerous successful chemotherapeutic agents. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). This line of cases demonstrates that the Board and the courts recognize the significant advances in cancer treatment in recent years.

The Examiner nevertheless contends that Applicants numerous *in vitro* examples in the specification are not enough. To the contrary, *in vitro* models are sufficient for establishing enablement of compositions, and often are sufficient to establish *in vivo* activity, even for method of treatment claims. *In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995); *see also* M.P.E.P. 2164.02. The Federal Circuit in *Brana* held that *in vitro* tumor models were sufficiently enabling for the treatment of cancer. Similarly, the *in vitro* data of HDAC inhibition, cytotoxicity in SQ-20B cells, and radiation clonigenic survival rates assays described in the instant specification sufficiently enable the use of the presently claimed compounds. *Specification* at Tables 3 and 4. As explained in the specification, HDAC inhibitors are known in the art as sensitizing agents in radiation therapy, *Specification* at p. 3. The data presented in Tables 3 and 4 confirm this fact. Accordingly, the presently claimed compounds would be expected to be useful in inhibition of HDAC activity, increasing sensitivity of cancer cells to the cytotoxic effects of radiation and the treatment of cancer. Thus, factors 3 and 5 also support enablement of the instant claims.

With respect to the fourth *Wands* factor, the ordinary artisan is highly skilled, as the Examiner previously noted. *Office Action mailed May 8, 2006*, at p. 3.

Regarding the sixth *Wands* factor, the Examiner states that the inventors provides "little direction in the instant specification," and further contends that that all of the compounds shown in

Tables 3 and 4 of the instant application have either a phenyl or adamantyl, and do not cover the scope of the claimed genus of aryl, cycloalkyl and heterocyclyl. *Final Office Action* at p. 3. To the contrary, examples 1-8, depicted in Tables 3 and 4, in fact include examples of both aryl and substituted aryl (e.g., dimethylaminophenyl), as well as cycloalkyl (e.g., adamantyl). In Applicants' previous response, Applicants pointed to synthetic scheme I (Specification p. 31), demonstrating that the preparation of such compounds has indeed been enabled. *Response mailed September 8, 2006*. This evidence establishes that those skilled in the art would readily know make the claimed compounds based on the guidance provided in the instant application. The Examiner has not denied that Scheme I, in addition to examples 1-8, sufficiently enable the skilled artisan to at least make the presently claimed compounds.

Nevertheless, the Examiner contends that the present rejection under § 112, first paragraph, is based on "make and use," and that Applicants allegedly have not enabled the use of these compounds because pharmaceutically uses are allegedly "unpredictable." *Final Office Action* at p. 3. As discussed above, Applicants data establishes HDAC inhibition, cytotoxicity and increased radiation sensitivity in compounds having aryl, substituted aryl and cycloalkyl groups, as well as compounds having varied values for m and n. *Specification* at Tables 3 and 4.

Regarding the seventh and eighth Wands factors, the Examiner states in the Advisory Action that Applicants data where R1 is phenyl or adamantyl "does not cover the scope of applicants generic claims of the aryl cycloalkyl or 3 to 10 membered hetero cycle." As explained in detail above, the specification provides many working examples, including *in vitro* data demonstrating HDAC inhibition, cytotoxicity in SQ-20B cells, and radiation clonigenic survival data for compounds encompassed by the instant claims. *Specification* at Tables 3 and 4. As discussed above, *in vivo* data is not required to establish enablement for *in vivo* treatment claims. *See In re Brana*, 51 F.3d. at 1565-6. Moreover, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. § 2164.01; *In re Brana*, 51 F.3d. at 1565-6.

Applicants again stress that the Examiner's analogy to caffeine and theophylline is inaccurate. *Advisory Action*; *Office Action mailed May 8, 2006*, at p. 3. The Examiner continues to

rely on this irrelevant and factually incorrect analogy, despite the references submitted by applicants in the previous response. In the previous response, Applicants demonstrated that theophylline and caffeine have both similar structure and activity. (See Snyder et al.; Chapman et al; and Wikipedia Attached to response filed March 26, 2007). These references demonstrate that the xanthine class of compounds, as a whole, possess similar biological activity. For example, Snyder et al. demonstrates that caffeine and theophylline have several biological activities in common, such as the reversal of L-PIA evoked depression and stimulation of locomotor activity (see Abstract and Fig. 1), and hypothesizes that the entire class of xanthines exhibits behavioral stimulant effects due to the blockade of central adenosine receptors (Abstract). Chapman et al. notes that caffeine "shares a variety of its pharmacological properties with the other naturally occurring methylxanthines, theophylline and theobromine. (Chapman at 616, ll. 2-17.) According to Wikipedia, theophylline "bears structural and pharmacological similarity to caffeine." (Wikipedia, Theophylline, at p. 1).

In response to this evidence, the Examiner applies a new standard. According to the Examiner "[c]affeine even though structurally so similar . . . is not marketed as a bronc[h]odilator." *Advisory Action*. Thus, the Examiner concludes that this example is still valid. That caffeine is not *marketed* as a bronchodilator does not negate the scientifically established fact that it has similar activity to theophylline. Thus, the theophylline/caffeine comparison demonstrates that, contrary to the Examiner's contention, those skilled in the art would expect the presently claimed genus of compounds to possess similar activity.

For at least the reasons set forth above, Applicants submit that the instant claims are fully enabled in accordance with 35 U.S.C. § 112, first paragraph.

III. Conclusion

In light of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone interview would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, GUX-012.01.**

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Respectfully submitted,

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